REMARKS

Claims 1-15 are pending.

No new matter has been added.

Rejections Under 35 USC § 103

The Examiner has rejected claim 6 as obvious over Maegerlein et al. as evidenced by Azarmi et al. in view of Pankhania et al. The Examiner contends that the Maegerlein et al. formulation combines torasemide with an acrylic polymer and also discloses xanthan gum and galactomannan as suitable polymers, but fails to specifically mention guar gum. The Examiner attempts to fill this void with the disclosure of Pankania et al., which she states teaches xanthan gum, guar gum and acrylic resins as polymers known for possessing sustained release properties. From this the Examiner concludes that the skilled artisan would be motivated to replace the exemplified acrylic polymer with guar gum. We assume that the Examiner means replacing the Eudragit acrylic polymer in Examples 8 and 9 of the Maegerlein et al. formulations with guar gum.

The Examiner has also rejected claims 1-15 as obvious over Berner et al. in view of Kaplan. The Examiner contends that the Berner et al. reference presents controlled release, gastric retentive dosage forms for oral administration and, while not showing a formulation containing torasemide, does list this as one of nine diuretic drugs that could be used. The Examiner also contends that this reference mentions fillers, binders and additives for tablet formulation for oral administration as well as the use of acrylic acid polymers, cellulose polymers, and guar gum as the polymer for sustained release. The Examiner admits that Berner et al. do not exemplify a formulation comprising torasemide. The Examiner then relies on Kaplan to provide the teaching that long-acting formulations are preferred and that torasemide is a longer-acting diuretic.

Applicants respectfully traverse.

Applicants first note that the Pankhania et al. reference states that the sustained release carrier comprises a major proportion of xanthan gum. Consequently, while Pankania et al. recite guar gum as one of many polymers having sustained release properties that can replace xanthan gum, there is no suggestion that the amount of guar gum would be different from the amount of xanhan gum used in the formulation.

As stated by Dr. Guglietta in the accompanying Declaration, lactose is a well known diluent which is normally used in immediate release formulation, not in controlled release formulations since it normally does not influence or control the release profile. On the contrary, it is sometimes used as a release enhancer. Therefore, in view of the teachings in the art as a whole, a skilled artisan would not have had a reasonable expectation of success in obtaining the instantly claimed invention which has controlled release by using lactose in the formulation.

To assist the Examiner in appreciating the instant invention, Applicants make the following points, summarized below from the Declaration of Dr. Guglietta. The present invention has a formulation containing torasemide, a matrix forming polymer and lactose as the main diluent. This results in a prolonged-release formulation of torasemide which shows a kinetic profile with fewer fluctuations and steadier levels. The percentage of lactose in the preferred formulations of the invention is about 50% of the blend (see examples 6-9). On the other hand, the matrix forming polymer is present in a small proportion in the formulation of the invention; normally less than 20% of the total composition, and more preferably from 2-5%.

Dr. Guglietta provides the following information to illustrate the kinetic profiles of examples of the torasemide formulations (tablets) of the claimed invention, Meyprogat® 90 (i.e. guar gum) at 10, 5 and 3% of the total tablet weight was tested as shown in the Table below for the 5 mg tablet dose (5 mg torasemide).

Formulation	T1604	T1704	T1804
Torasemide	5.9 %	5.9 %	5.9 %
Corn starch	36.2 %	36.2 %	36.2 %
Colloidal Silicon Dioxide	0.5 %	0.5 %	0.5 %
Meyprogat® 90	10.0%	5.0 %	3.0 %
Magnesium stearate	0.3 %	0.3 %	0.3 %
Lactose	47.1%	52.1 %	54.1 %

The following dissolution tests were performed with hydrochloric acid 0.1 N.

Dr. Guglietta notes that in comparison with Sutril® (Immediate release formulation), the experimental tablets showed a prolonged release behaviour starting from 3% of guar gum (batch T1804). The total release of the active in this batch (T1804) was produced in 5 hours. Batches with 5% and 10% of the excipient (i.e. T1704 and T1604) presented a 75% active release within 5 hours with a similar kinetic profile. The following table and figure show the results of the kinetic profile of these formulations.

	Sutril 5 mg		Batch T1604		Batch T1704		Batch T1804	
Time (min)	Release per time fraction %	Release %	Release per time fraction %	Release %	Release per time fraction %	Release %	Release per time fraction %	Release %
0	-	0	-	0	-	0	-	0
0.5	98.2	98.2	22.5	22.5	23.4	23.4	26.6	26.6
1	2.3	100.5	10.2	32.7	7.2	30.6	7.4	34.1
2	0.4	101.3	7.5	47.7	6.4	43.5	12.7	59.6
3	-0.6	100.1	5.7	59.0	5.7	54.8	12.8	85.1
4	-0.3	98.9	3.7	73.9	6.1	79.1	3.1.	97.5

Table. Release values (with HCl 0.1N) for tablets manufactured with Meyprogat® 90.

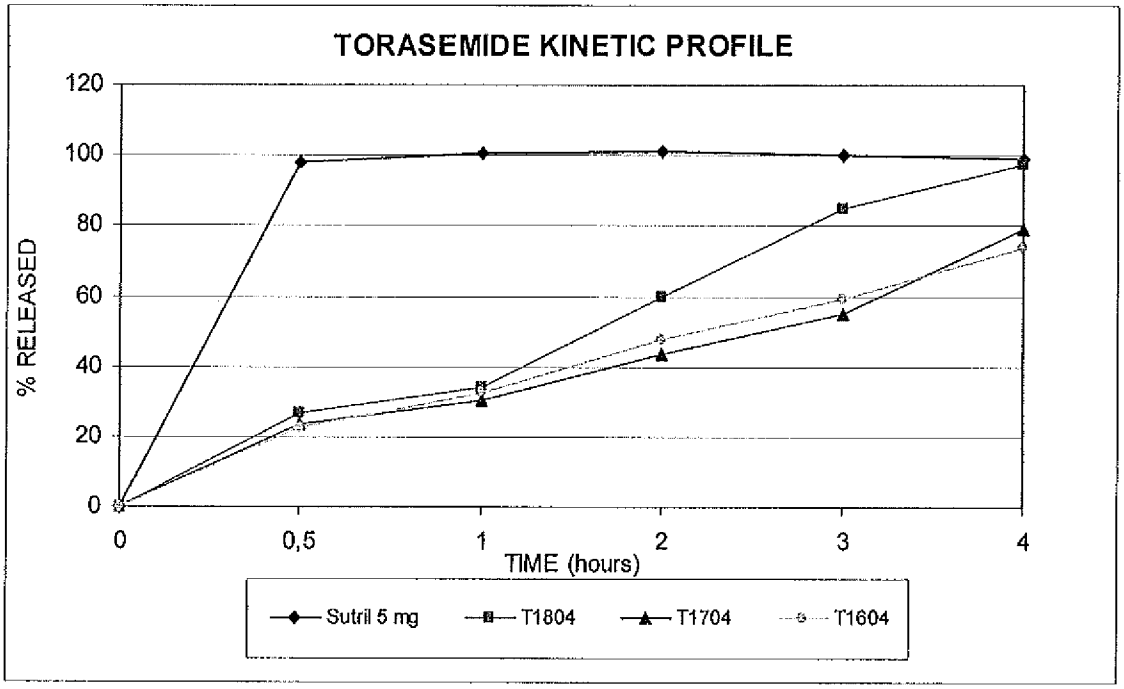

Figure. *Release profiles (with HCl 0.1N) of Torasemide from Meyprogat® 90matrix tablets.*

The percentage of lactose in the experiments is above 45% with respect of the blend. The amount of guar gum is less than 10% of the amount of lactose.

Thus, in view of the above discussion, Applicants submit that the instant invention is not obvious over the cited prior art and respectfully request removal of the rejection.

Conclusion

In view of the above remarks, all of the claims are submitted as defining non-obvious, patentable subject matter. Reconsideration of the rejections and allowance of the claims are respectfully requested. Applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Susan W. Gorman, Ph.D. Reg. No.

47,604 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: September 10, 2010

Respectfully submitted,

#47,604

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Enclosures: Declaration by Dr. Antonio Guglietta